

(10)



Eur. Pat. Amt  
European Patent Office  
Office européen des brevets

(11) Publication number:

0 092 968  
A1

(12)

# EUROPEAN PATENT APPLICATION

(21) Application number: 83302238.7

(22) Date of filing: 20.04.83

(61) Int. Cl.<sup>3</sup>: C 07 D 519/00  
C 07 D 499/22, A 61 K 31/43  
/(C07D519/00, 499/00, 499/00)

(30) Priority: 23.04.82 US 371156

(43) Date of publication of application:  
02.11.83 Bulletin 83/44

(84) Designated Contracting States:  
AT BE CH DE FR GB IT LI LU NL SE

(71) Applicant: PFIZER INC.  
235 East 42nd Street  
New York, N.Y. 10017(US)

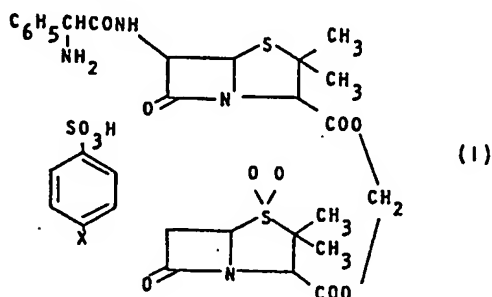
(72) Inventor: Barth, Wayne Ernest  
40 Monticello Drive  
East Lyme Connecticut(US)

(72) Inventor: Jasys, Vytautas John  
15 Richmond Street  
New London Connecticut(US)

(74) Representative: Graham, Philip Colin Christison et al,  
Pfizer Limited Ramsgate Road  
Sandwich, Kent CT13 9NJ(GB)

(64) Crystalline benzenesulfonate salts of sultamicillin.

(57) Novel benzenesulfonic acid addition salts of sultamicillin  
of the formula



and hydrated forms thereof, where X is hydrogen or chloro, especially the crystalline dihydrate salts, having advantages over the prior art forms of sultamicillin in pharmaceutical dosage forms, most particularly those for use in pediatric medicine.

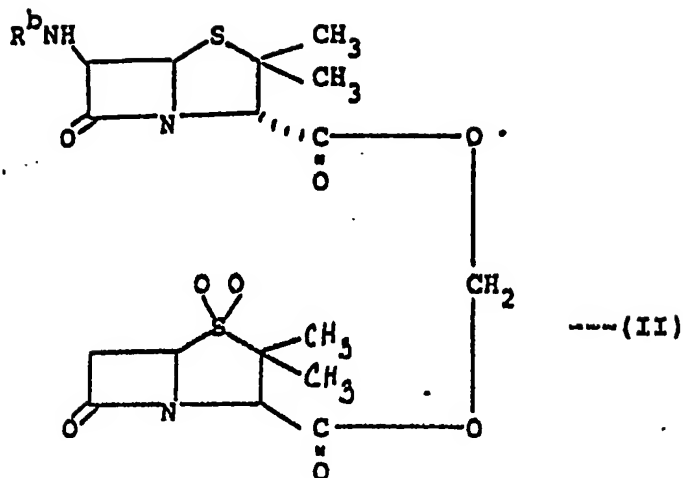
EP 0 092 968 A1

CRYSTALLINE BENZENESULFONATE  
SALTS OF SULTAMICILLIN

The invention relates to certain novel benzene-sulfonic acid addition salts of 1,1-dioxopenicillanoyl-oxymethyl 6-[D-(2-amino-2-phenylacetamido)]penicillanate (sultamicillin) having advantages for use in antibacterial formulations.

Barth, in U.S. 4,234,579 issued November 18, 1980, discloses penicillanic acid 1,1-dioxide (sulbactam) and esters thereof which are readily hydrolyzable in vivo, useful as antibacterial agents and for enhancing the effectiveness of beta-lactam antibiotics, such as ampicillin, against many beta-lactamase producing bacteria.

Bigham, in U.S. 4,244,951 issued January 13, 1981; and Netherland Patent Application No. 8,000,775 published August 15, 1980, corresponding to British Patent Application No. 2,044,255, both disclose novel conjugates of penicillanic acid 1,1-dioxide with known penicillin antibiotics which are linked via a methylene-dioxy group. These conjugates are of the general formula



wherein  $R^b$  is the acyl group of a natural or semi-synthetic penicillin.

The compound of the above formula wherein  $R^b$  is D-(2-amino-2-phenylacetyl) is designated herein as "sultamicillin" and will be referred to herein by that name. It is a methylenedioxy linked conjugate of penicillanic acid 1,1-dioxide and ampicillin.

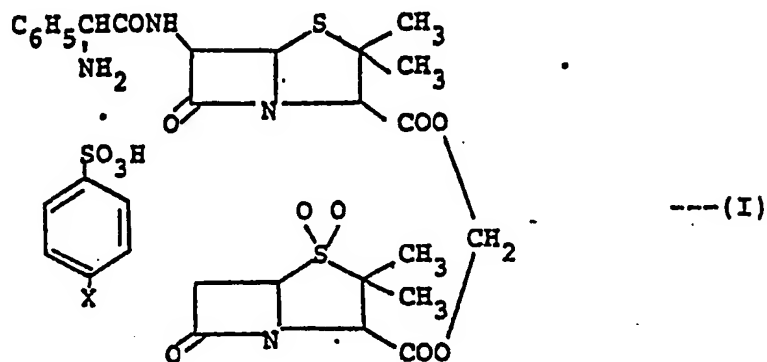
Sultamicillin free base has been found to have poor handling characteristics and inadequate stability. The only salt of sultamicillin specifically disclosed in the art is the hydrochloride. While it is suitable for certain antibacterial formulations, it also has poor solid state stability, which is reflected in handling difficulties, and is highly soluble in water in which it is subject to hydrolytic decomposition. Thus, it is unsuitable for aqueous dosage formulations, including the aqueous suspensions preferred in pediatric medicine.

Crystalline forms of compounds are ordinarily preferable to the non-crystalline forms thereof. The crystalline materials have superior stability, appearance and handling characteristics when compared to their amorphous counterparts. For pharmaceutical use crystalline compounds are especially advantageous in manufacturing procedures and in formation and use of acceptable dosage forms such as solutions, suspensions, elixirs, tablets, capsules and various pharmaceutically elegant preparations required by the medical and pharmaceutical professions.

For pediatric administration it is well recognized by those of skill in the art that solutions or liquid suspensions are highly preferable dosage forms. Tablets and capsules are difficult for children to swallow and the amount of drug delivered is not as flexible as is often required for pediatric drugs. With liquid dosage forms, by contrast, the amount of drug delivered to the patient can be varied over a wide range merely by regulating the volume of dose of known concentrations.

Conjugate antibiotics such as sultamicillin are susceptible to partial hydrolysis to its components (ampicillin and sulbactam) upon storage in aqueous media. Thus, the enhanced stability in aqueous suspensions of a salt of sultamicillin of limited solubility, relative to another salt of significantly higher solubility, such as the hydrochloride, is evident.

The invention relates to certain benzenesulfonic acid addition salts of sultamicillin of the formula



- 5 and hydrated forms thereof, where X is hydrogen or  
chloro. Especially preferred salts of formula (I) are  
the crystalline dihydrates. These crystalline salts  
have advantages over prior art forms of sultamicillin  
and other salts of this conjugate antibacterial agent.
- 10 The crystalline dihydrate salts of the invention have  
excellent pharmacokinetic properties, near optimal  
solubility in aqueous systems and improved stability  
in bulk and in aqueous suspensions. As a result of  
these features, the crystalline salts of the invention
- 15 offer valuable advantages in manufacture of various  
dosage forms, particularly pediatric dosage forms, and  
in improving product stability.

The invention also provides the anhydrous and other hydrated forms of the same salts of formula (I) which serve as precursors of the more desirable crystalline dihydrates.

5       The invention also provides pharmaceutical compositions suitable for treating a bacterial infection in a mammalian subject comprising an antibacterially effective amount of a crystalline dihydrate salt of the invention and a pharmaceutically acceptable carrier. Particularly  
10       preferred such compositions are those suitable for use in pediatric medicine.

      Further, the invention provides a method for treating a bacterial infection in a mammalian subject, especially a child, which comprises administering to  
15       said subject an antibacterially effective amount of a salt of the invention.

---

The salts of formula (I) are prepared by standard methods known in the art for preparing acid addition salts of aminopenicillins. For example, they are obtained by contacting the free base of sultamicillin, or an acid addition salt thereof, with an equimolar amount of the appropriate acid, i.e., benzenesulfonic acid or 4-chlorobenzenesulfonic acid in the presence of a suitable solvent. By the term "suitable solvent" is meant a solvent that will not appreciably react with the reactants or product, under the conditions employed, except to form a solvate, will dissolve or partially dissolve the reactants at or about room temperature and will allow precipitation of the product salt at room temperature or below, or upon addition of a non-solvent. Examples of suitable solvents include ethyl acetate, methanol, ethanol, butanol, acetone, methylethyl ketone, tetrahydrofuran, water and mixtures thereof. The sultamicillin free base can be obtained, e.g., by methods described in U.S. 4,244,951 and Great Britain Patent Application No. 2,044,255. The starting benzenesulfonic acids are readily available in commerce.

The compounds of formula (I) can also be prepared by metathesis of salt forms in which an inorganic salt is formed, for example, by reaction of a hydrohalide addition salt of sultamicillin with an alkali metal or alkaline earth salt of the appropriate sulfonic acid. In a preferred such reaction, sultamicillin hydrochloride is reacted with sodium benzenesulfonate or sodium 4-chlorobenzenesulfonate in water, from which the particularly preferred crystalline dihydrate salt of formula (I) is precipitated and, if desired further purified, e.g. by recrystallization.

A further method for forming the instant salts of formula (I) is by reaction of an amino-protected precursor of sultamicillin in the presence of the requisite benzenesulfonic acid or 4-chlorobenzenesulfonic acid under conditions which both remove the amino-protecting group and allow salt formation. In a preferred such reaction an enamine-protected precursor of sultamicillin, e.g. 1,1-dioxopenicillanoyloxymethyl 6-[D-(2-[1-methyl-2-methoxycarbonylvinylamino]-2-phenylacetamido)]penicillanate is contacted with an equimolar amount of benzenesulfonic acid or 4-chlorobenzenesulfonic acid in the presence of a polar organic solvent, e.g., ethyl acetate, and water. Under these conditions and at or about room temperature, the enamine protecting group is removed, the desired salt is formed and it precipitates from solution, ordinarily as the crystalline dihydrate.

When salt formation is carried out under anhydrous conditions, the product formed is an anhydrous compound of formula (I). When the amount of water used is less than that needed to form the dihydrate mixtures of the anhydrous, monohydrate and dihydrate forms are produced. The anhydrous salts and monohydrates of formula (I) are useful as intermediates leading to the more stable dihydrates upon exposure to moisture.



The crystalline dihydrate salts of the invention have advantageous properties which make them particularly useful as orally administered antibacterial agents. They allow rapid absorption from the gastrointestinal tract. During or subsequent to absorption, in vivo ester hydrolysis occurs with liberation of ampicillin and the beta-lactamase inhibitor, penicillanic acid 1,1-dioxide (sulbactam). These salts have relatively low, yet adequate, solubility in aqueous systems, resulting in improved stability of aqueous oral dosage forms, such as the oral suspensions preferred in pediatric medicine.

#### Pharmacokinetic Studies

Upon oral administration to laboratory animals the crystalline invention compounds and the hydrochloride salt are each found to have excellent pharmacokinetic properties. The results of such a study conducted in rats is summarized in Table I, below. The data shows that each of the three salts are rapidly absorbed and hydrolyzed upon oral administration to produce high serum levels of both ampicillin and the beta-lactamase inhibitor, sulbactam. The differences between the three salts summarized in Table I are found to be not significant, statistically.

Table I. Pharmacokinetic Data After Oral Administration of 20 mg./kg. of Sultamicillin Salt to Rats

Sample Time, Hr.	Serum Concentration ( $\mu\text{g./ml.}$ )					
	Hydrochloride Salt		$\text{C}_6\text{H}_5\text{SO}_3\text{H}\cdot 2\text{H}_2\text{O}$ Salt		$4\text{-ClC}_6\text{H}_4\text{SO}_3\text{H}\cdot 2\text{H}_2\text{O}$ Salt	
	Ampicillin	Sulbactam	Ampicillin	Sulbactam	Ampicillin	Sulbactam
0.25	1.74 $\pm$ 0.15	1.51 $\pm$ 0.27	1.77 $\pm$ 0.17	1.15 $\pm$ 0.13	2.65 $\pm$ 0.26	2.21 $\pm$ 0.32
0.5	1.99 $\pm$ 0.17	2.15 $\pm$ 0.30	2.25 $\pm$ 0.16	1.47 $\pm$ 0.20	2.88 $\pm$ 0.03	2.29 $\pm$ 0.24
1	1.39 $\pm$ 0.12	1.46 $\pm$ 0.12	1.31 $\pm$ 0.07	1.00 $\pm$ 0.11	1.47 $\pm$ 0.18	1.13 $\pm$ 0.12
1.5	0.87 $\pm$ 0.11	1.00 $\pm$ 0.16	0.80 $\pm$ 0.01	0.67 $\pm$ 0.11	0.81 $\pm$ 0.07	0.73 $\pm$ 0.05
2	0.5 $\pm$ 0.07	0.71 $\pm$ 0.13	0.55 $\pm$ 0.03	0.49 $\pm$ 0.07	0.39 $\pm$ 0.06	0.39 $\pm$ 0.03
3	0.25 $\pm$ 0.04	0.42 $\pm$ 0.08	0.26 $\pm$ 0.02	0.34 $\pm$ 0.05	0.15 $\pm$ 0.03	0.16 $\pm$ 0.03
4	0.13 $\pm$ 0.02	0.17 $\pm$ 0.04	0.15 $\pm$ 0.01	0.22 $\pm$ 0.02	0.06 $\pm$ 0.007	0.08 $\pm$ 0.01
Area Under Serum Curve, $\mu\text{g./ml. hr.}$	3.19	3.96	3.28	2.91	3.42	2.92
T 1/2, Beta-phase, hr.	0.87	1.18	0.91	1.26	0.63	0.73

-10-

The above data was obtained employing 80-100 g. out-bred Sprague-Dawley rats. The compounds are administered orally (5 rats per compound) as an aqueous suspension, 0.5 ml., containing 20 mg./kg. of the drug.

Blood samples are taken at the indicated times and subjected to differential bioassay to determine the ampicillin and sulbactam levels. The ampicillin bioassay makes use of Sarcina lutea (ATCCC 9341) which is susceptible to ampicillin but insensitive to sulbactam at concentrations as high as 100 µg./ml., since it does not contain a beta-lactamase. Thus, this organism fails to show synergy with combinations of ampicillin and sulbactam. A standard curve is prepared in normal serum at ampicillin levels of 4, 2, 1, 0.5, 0.25 and 0.125 µg.ml. Sterile filter paper discs are loaded with 25 lambda volumes. Assay plates are prepared using seed agar (Difco). An overnight culture of Sarcina lutea is diluted 1:100 and 1 ml. of this dilution is added to 100 ml. of the agar in 12/12" plastic plates. The plates are then incubated at 37°C. for 18 hours, and the zones measured.

The sulbactam determination is based on the insensitivity of Pasteurella histolytica (59B010) to high concentrations of either ampicillin or sulbactam, alone. However, since its resistance is mediated via a beta-lactamase, the culture responds synergistically to combinations of ampicillin and sulbactam. A standard curve is prepared in a manner analogous to that described above for ampicillin. Assay plates are prepared by adding 1 ml. of an overnight culture of Pasteurella histolytica to 100 ml. of Mueller-Hinton agar that has been adjuncted with 50 µg./ml. ampicillin and 5% sterile bovine blood. The plates are incubated at 37°C. for about 18 hours after which the zones are measured.

15 Solubility

The solubility of the salts in water and simulated gastric juice without pepsin (pH 1.2) were compared. Equilibrium solubility was not determined since the compounds are not entirely stable in aqueous systems for the extended time required to reach equilibrium. Therefore, the apparent solubility was determined by vigorous agitation for 30 minutes with the solvent. The resulting mixture was then filtered and the amount of compound in solution determined by high pressure liquid chromatography (HPLC). The results are summarized in Table II.

Table II  
 Apparent Solubility of Sultamicillin  
 Salts in Water and Simulated Gastric Juice  
 (Without Pepsin, pH 1.2)

	<u>Salt</u>	<u>Apparent Solubility, mg/ml</u>			
		<u>Water</u>	<u>(Final pH)</u>	<u>Simulated Gastric Juice</u>	<u>(Final pH)</u>
5	Hydrochloride	>94	(2.0)	>79	(1.12)
10	Benzenesulfonate.2H <sub>2</sub> O*	2.15	(3.4)	1.8	(2.0)
	4-Chlorobenzene-sulfonate.2H <sub>2</sub> O*	3.3	(3.8)	6.3	(1.1)
	*crystalline				

Crystallinity

X-ray powder diffraction patterns were obtained on a Siemens diffractometer equipped with copper radiation and a scintillation counter detector. Beam intensity as a function of the angle  $2\theta$  was recorded at a scanning rate of  $2^\circ$  per minute. The crystallinity of sultamicillin benzenesulfonate dihydrate and sultamicillin 4-chlorobenzenesulfonate dihydrate were verified by a multiplicity of peaks in the x-ray powder diffraction patterns for these salts.

Stability

Upon storage of samples of the three salts at  $50^\circ\text{C}$ . for three weeks the crystalline benzenesulfonate. $2\text{H}_2\text{O}$  and 4-chlorobenzenesulfonate. $2\text{H}_2\text{O}$  were found to have retained 97% and 100% of their potency, respectively. The hydrochloride salt retained only 67% of its original potency under these conditions.

High Pressure Liquid Chromatography (HPLC)

In the solubility and stability studies above samples of the materials were assayed by HPLC using a Chromegabond C-8\* column (4.6 mm internal diameter x 30 cm.). The mobile phase consisted of 30% by weight acetonitrile in pH 3 phosphate buffer (0.1 M). Flow rate, 1.6 ml/minute. Detection was by UV at 230 nm.

\*A trademark of ES Industries.

-14-

When using an antibacterial salt of this invention in a mammal, particularly man, the compound can be administered alone, or it can be mixed with other antibiotic substances and/or pharmaceutically-acceptable carriers or diluents. Said carrier or diluent is chosen on the basis of the intended mode of administration. For example, when considering the oral mode of administration, an antibacterial compound of this invention can be used in the form of tablets, capsules, lozenges, troches, powders, syrups, elixirs, aqueous solutions and suspensions, and the like, in accordance with standard pharmaceutical practice. The proportional ratio of active ingredient to carrier will naturally depend on the chemical nature, solubility and stability of the active ingredient, as well as the dosage contemplated. In the case of tablets for oral use, carriers which are commonly used include lactose, sodium citrate and salts of phosphoric acid. Various disintegrants such as starch, and lubricating agents, such as magnesium stearate, sodium lauryl sulfate and talc, are commonly used in tablets. For oral administration in capsule form, useful diluents are lactose and high molecular weight polyethylene glycols, e.g. polyethylene glycols having molecular weights of from 2000 to 4000.

Because of the advantageous solubility and stability of the crystalline sultamicillin benzene-sulfonate dihydrate salts of the invention, a particularly preferred mode of administration for use with children is orally via an aqueous suspension. For preparing such suspensions the crystalline dihydrate of formula (I) can be combined with buffers, emulsifying and suspending agents. If desired, certain sweetening and/or flavoring agents can be added. The resulting suspension can be stored in the presence of water, especially if refrigerated, for considerable periods. However, a preferred method is to store the mixture as a dry powder until its use is required, at which time it is mixed with an appropriate diluent, e.g., water.

As indicated earlier, the antibacterial compounds of this invention are of use in human subjects and the daily dosages to be used will not differ significantly from other, clinically-used, penicillin antibiotics. The prescribing physician will ultimately determine the appropriate dose for a given human subject, and this can be expected to vary according to the age, weight, and response of the individual patient as well as the nature and severity of the patient's symptoms. The compounds of this invention will normally be used orally at dosages in the range from about 20 to about 100 mg. per kilogram of body weight per day, and parenterally at dosages from about 10 to about 100 mg. per kilogram of body weight per day, usually in divided doses. In some instances it may be necessary to use doses outside these ranges.



The following examples and preparations are provided solely for further illustration. Infrared (IR) spectra were measured as potassium bromide discs (KBr discs) and diagnostic absorption bands are reported in wave numbers ( $\text{cm}^{-1}$ ). Nuclear magnetic resonance spectra (NMR) were measured at 60 MHz for solutions in deuterated chloroform ( $\text{CDCl}_3$ ) or deuterated dimethyl sulfoxide ( $\text{DMSO}-d_6$ ), and peak positions are reported in parts per million downfield from tetramethylsilane. The following abbreviations for peak shapes are used: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet.

EXAMPLE 1

1,1-Dioxopenicillanoyloxymethyl  
6-[D-(2-amino-2-phenylacetamido)]-  
penicillanate benzenesulfonate dihydrate

5 To 6.31 g. (0.01 mole) 1,1-dioxopenicillanoyloxy-  
methyl 6-[D-(2-amino-2-phenylacetamido)]penicillanate  
hydrochloride is added 40 ml. water and the mixture  
is stirred for about 15 minutes. Insoluble material  
(ca. 0.75 g. of gum) is removed by filtration and to  
10 the filtrate is added a solution of 1.58 g. (0.01 mole)  
benzenesulfonic acid in 10 ml. water. The resulting  
gummy mixture is stirred with a glass rod until the  
salt hardens and breaks up into small lumps. Stirring  
is continued for one hour (magnetic stirrer) after  
15 which the solid is collected by filtration and washed  
well with water. The washed solid is dried under  
nitrogen to afford 5.8 g. (77%) of colorless product,  
M.P. 138°C. (decomp.). <sup>1</sup>H-NMR (DMSO-d<sub>6</sub>) ppm (delta):  
1.38 (s, 6H), 1.45 (s, 6H), 3.0-3.9 (m, 2H), 4.4 (s,  
1H), 4.5 (s, 1H), 4.95-5.28 (m, 2H), 5.3-5.66 (m,  
2H), 5.89 (s, 2H), 7.15-7.75 (m, 10H); infrared  
20 spectrum: (Nujol\*) broad band at 1805-1770 cm<sup>-1</sup>.

X-ray powder diffraction: peaks, degrees  
2 theta: 9.3, 11.4, 12.2, 13.4, 15.5, 16.2, 16.9,  
25 17.1, 18.3, 18.9, 19.8, 20.6, 22.3, 22.7, 23.4, 25.4,  
26.7, 27.3, 29.6, 30.5, 31.7, 33.5, 34.4, 35.1, 36.1,  
37.5, 38.6 and 44.7.

\*Trademark for Plough Inc. brand of Mineral Oil.

EXAMPLE 2

1,1-Dioxopenicillanoyloxymethyl 6-[D-(2-amino-2-phenylacetamido)]penicillanate  
4-chlorobenzenesulfonate dihydrate

5 To a solution of 15 g. (25.25 mmole) 1,1-dioxo-  
penicillanoyloxymethyl 6-[D-(2-amino-2-phenylacet-  
amido)]penicillanate in 150 ml. ethyl acetate is  
added over ten minutes a solution of 4.85 g. (25.25  
10 mmole) 4-chlorobenzenesulfonic acid in 25 ml. ethyl  
acetate and 6 ml. water. After the addition is  
complete, an additional 50 ml. ethyl acetate is added  
and the resulting mixture is stirred at room tempera-  
ture overnight. The colorless crystals are collected  
by filtration, the cake slurried in 200 ml. ethyl  
15 ether and filtered again. Upon drying in air 13.7 g.  
of colorless crystals are obtained.

Ten grams of crystals are dissolved in 100 ml.  
methanol at room temperature. Water is added to the  
cloud point (ca. 200 ml.). The resulting hazy  
20 solution is stirred at room temperature for two hours  
during which time the product crystallizes. Upon  
filtration and air drying overnight, 7.5 g. of  
product is obtained.  $^1\text{H-NMR}$  (DMSO- $d_6$ ) ppm (delta):  
1.36 (s, 6H), 1.47 (s, 6H), 3.34 (broad, 5H), 3.74  
25 (dd, 1H,  $J = 4 \text{ Hz}, 17 \text{ Hz}$ ), 4.40 (s, 1H), 4.51 (s,  
1H), 5.08 (m, 2H), 5.48 [m, 2H, ( $J_{ABq} = 4 \text{ Hz}$  upon  $\text{D}_2\text{O}$   
overlay)], 5.86 (s, 2H), 7.45 (m, 9H).

Analysis Calculated for  $\text{C}_{31}\text{H}_{35}\text{O}_{12}\text{N}_4\text{S}_3\text{Cl}\cdot 2\text{H}_2\text{O}$ :  
C, 45.22; H, 4.77; N, 6.81; S, 11.68; Cl, 4.31  
30 Found: C, 45.04; H, 4.83; N, 6.86; S, 11.74; Cl, 4.27.

Water (Karl Fischer) 4.98 (Theory, 4.37).

X-ray powder diffraction: peaks, degrees  
2 theta: 8.9, 10.8, 11.3, 13.2, 15.5, 16.0, 17.1,  
18.0, 19.3, 20.0, 22.4, 22.7, 23.3, 26.0, 27.9, 30.0,  
35 30.5, 34.1, 34.5, 35.9, 37.5, 38.5 and 44.8.

EXAMPLE 3

A solution of 64.1 g. (0.108 mole) 1,1-dioxo-  
penicillanoyloxymethyl 6-[D-(2-amino-2-phenylacetamido)]-  
penicillanate in 1400 ml. ethyl acetate (apparent pH  
5 7.6) is adjusted to pH 2.5 by addition of 325 ml. of  
a solution of 18.0 g. benzenesulfonic acid (90%  
technical grade) in 400 ml. ethyl acetate. The  
resulting pale yellow slurry is cooled to 5°C. and  
granulated for 60 minutes at this temperature. The  
10 resulting slurry is washed with an equal volume of  
water, the layers separated and the ethyl acetate  
layer is cooled to 5°C. The resulting thick white  
slurry is filtered, the cake washed with hexane (4 x  
100 ml.) and dried in vacuo at 35°C. overnight to  
15 afford 42 g. of crystalline benzenesulfonate salt  
which assayed 4.67% water (Karl Fischer method); %  
volatiles (60°C., 3 hours in vacuo), 5.00%.

Analysis, Calculated for  $C_{31}H_{36}O_{12}N_4S_3 \cdot 2H_2O$ :

C, 47.20; H, 5.11; N, 7.10; S, 12.19.

20 Found: C, 47.14; H, 5.21; N, 7.12; S, 11.92.

EXAMPLE 4Oral Suspension

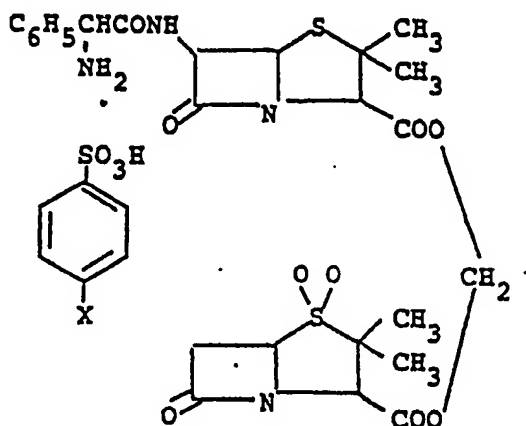
A dry blend of the following ingredients is prepared:

5		<u>Grams</u>
	Sultamicillin benzenesulfonate dihydrate, crystalline	6.80
	Sucrose	20.00
	Mannitol	10.00
10	Sodium citrate	0.40
	Hydrated aluminum magnesium silicate powder (Veegum S)	5.00
	Kaolin	2.00
	Sodium saccharin	2.00
15	Artificial flavor, powder	0.10

The dry blend is stored in sealed containers until needed, at which time it is diluted to 100 ml. volume with water. The suspension contains the equivalent of 50 mg./ml. of sultamicillin.

CLAIMS

1. A benzenesulfonic acid addition salt of sultamicillin of the formula



and hydrated forms thereof, wherein X is hydrogen or chloro.

2. A crystalline dihydrate salt according to claim 1.

3. The crystalline dihydrate salt according to claim 2 wherein X is hydrogen, having the following X-ray powder diffraction peaks:

<u>Peak, degrees 2 theta</u>		
9.3	19.8	30.5
11.4	20.6	31.7
12.2	22.3	33.5
13.4	22.7	34.4
15.5	23.4	35.1
16.2	25.4	36.1
16.9	26.7	37.5
17.1	27.3	38.6
18.3	29.6	44.7
18.9		

4. The crystalline salt according to claim 2 wherein X is chloro, having the following X-ray powder diffraction peaks:

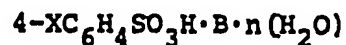
<u>Peak, degrees 2 theta</u>		
8.9	19.3	30.5
10.8	20.0	34.1
11.3	22.4	34.5
13.2	22.7	35.9
15.5	23.3	37.5
16.0	26.0	38.5
17.1	27.9	44.8
18.0	30.0	

5. A pharmaceutical composition suitable for treating a bacterial infection in a mammalian subject, which comprises an antibacterially effective amount of a compound according to claim 2 and a pharmaceutically acceptable carrier.

6. A pharmaceutical composition according to claim 5 suitable for pediatric use.

CLAIMS FOR AUSTRIA

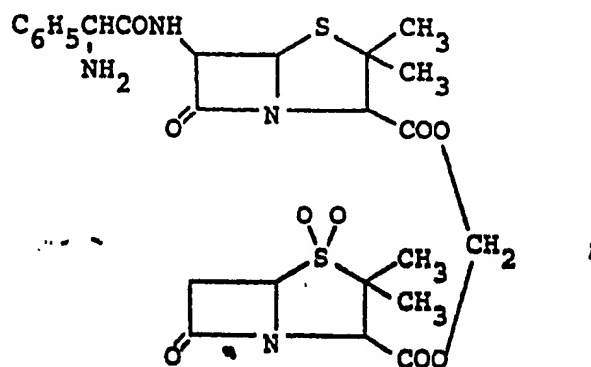
1. A process for preparation of a benzene-sulfonic acid addition salt of sultamicillin of the formula



where n is 0-2

X is hydrogen or chloro and

B is



characterized in that:

(a) the free base of formula B or an acid addition salt thereof is contacted with a benzenesulfonic acid of formula 4-XC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>H in the presence of a suitable solvent; or

(b) an acid addition salt of formula B·HY where Y is Cl, Br or I, is contacted with a benzenesulfonic acid salt of the formula 4-XC<sub>6</sub>H<sub>4</sub>SO<sub>3</sub>M, where M is an alkali metal or alkaline earth cation, in the presence of water.

2. A process according to claim 1 when carried out at room temperature or below.



3. A process according to claim 1 wherein n is 2.
  4. A process according to claim 1, part (b),  
wherein Y is Cl and M is Na.
  5. A process according to claim 3 wherein X is  
hydrogen and a crystalline dihydrate benzenesulfonic acid  
addition salt is obtained.
  6. A process according to claim 3 wherein X is  
chloro and a crystalline dihydrate benzenesulfonic acid  
salt is obtained.
-



European Patent  
Office

**PARTIAL EUROPEAN SEARCH REPORT**  
which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

**0092968**

Application number

DOCUMENTS CONSIDERED TO BE RELEVANT			EP 83 30 2238
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (Int. Cl. 2)
Y	GB - A - 2 084 572 (LØVENS)  * claims 1-18 *	1,6	C 07 D 519/00 499/22 A 61 K 31/43// (C 07 D 519/00 499/00 499/00)
P,Y	FR - A - 2 493 322 (SARATH)  * claims *	1,2,6	
			TECHNICAL FIELDS SEARCHED (Int. Cl. 2)
<b>INCOMPLETE SEARCH</b>  The Search Division considers that the present European patent application does not comply with the provisions of the European Patent Convention to such an extent that it is not possible to carry out a meaningful search into the state of the art on the basis of some of the claims. Claims searched completely: 1-4, 6 Claims searched incompletely: 5 Claims not searched: 5 Reason for the limitation of the search:  Method for treatment of the human or animal body by surgery or therapy (see article 52(4) of the European Patent Convention)			C 07 D 519/00 499/00 A 61 K 31/00
Place of search		Date of completion of the search	Examiner
The Hague		01-07-1983	CHOULY
CATEGORY OF CITED DOCUMENTS X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

**This Page is Inserted by IFW Indexing and Scanning  
Operations and is not part of the Official Record**

**BEST AVAILABLE IMAGES**

Defective images within this document are accurate representations of the original documents submitted by the applicant.

Defects in the images include but are not limited to the items checked:

- ☐ **BLACK BORDERS**
- ☐ **IMAGE CUT OFF AT TOP, BOTTOM OR SIDES**
- ☐ **FADED TEXT OR DRAWING**
- ☐ **BLURRED OR ILLEGIBLE TEXT OR DRAWING**
- ☐ **SKEWED/SLANTED IMAGES**
- ☐ **COLOR OR BLACK AND WHITE PHOTOGRAPHS**
- ☐ **GRAY SCALE DOCUMENTS**
- ☒ **LINES OR MARKS ON ORIGINAL DOCUMENT**
- ☐ **REFERENCE(S) OR EXHIBIT(S) SUBMITTED ARE POOR QUALITY**
- ☐ **OTHER:** \_\_\_\_\_

**IMAGES ARE BEST AVAILABLE COPY.**

**As rescanning these documents will not correct the image problems checked, please do not report these problems to the IFW Image Problem Mailbox.**